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on 18th December, 2010

By: _____

Printed: Matthew R. Kaser

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Barbas et al.

Title: Integrin $\alpha_{IIb}\beta_3$ Specific Antibodies and Peptides

Serial No.: 10/581,431 Filing Date: 3rd December, 2004

Examiner: HADDAD, Maher M. Group Art Unit: 1644

Mail Stop Amendment
Commissioner For Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO RESTRICTION REQUIREMENT

Dear Sir:

This communication is in response to the Restriction Requirement mailed 18th October, 2010, in the above-referenced application. This response filed with a Request for a (1) one-month extension of time, thereby allowing Applicants until 20h December 2010 to respond, the 18th December being a Saturday.

Election/Restrictions

Claims 1-32 were originally filed. In the Office Action, the Examiner stated that restriction is required under 35 U.S.C. § 121 and § 372. In addition, the Examiner stated that the inventions are not so linked as to form a single inventive concept under PCT Rule 13.1 and in accordance with 37 C.F.R. § 1.499 requested Applicant to elect claims corresponding to one of the following inventions:

Group I	Claims 1-4, 21, 24 and 27, drawn to an isolated and purified peptide.
Group II	Claims 5-10, 15-16, 22-23, 25-26, and 28-29, drawn to an antibody.
Group III	Claims 17-20, drawn to an isolated and purified polynucleotide encoding a peptide.
Group IV	Claims 11 and 30, drawn to a method of inhibiting platelet aggregation using a peptide.
Group V	Claims 12, 14, and 31-32, drawn to a method of inhibiting platelet aggregation using an antibody.
Group VI	Claim 13, drawn to a method of inhibiting binding of fibrinogen .to platelets using a peptide.

In response to the Examiner's Restriction Requirement Applicants provisionally elect Group II (claims 5-10, 15-16, 22-23, 25-26, and 28-29).

35 U.S.C. 121 ("Divisional applications") states:

> "If two or more independent and distinct inventions are claimed in one application, the Director may require the application to be restricted to one of the inventions."

35 U.S.C. 372 ("National stage: Requirements and procedure") states:

> "(a) All questions of substance and, within the scope of the requirements of the treaty and Regulations, procedure in an international application designating the United States shall be determined as in the case of national applications regularly filed in the Patent and Trademark Office."

PCT Rule 13.1 ("Requirement") states:

> "The international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention")."

PCT Rule 13.2 ("Circumstances in Which the Requirement of Unity of Invention Is to Be Considered Fulfilled") states:

> "Where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art."

Annex B ("Unity of Invention") of the Administrative Instructions of the PCT states:

> "(a) Unity of Invention. Rule 13.1 deals with the requirement of unity of invention and states the principle that an international application should relate to only one invention or, if there is more than one invention, that the inclusion of those inventions in one international application is only permitted if all inventions are so linked as to form a single general inventive concept."
>
> "(b) Technical Relationship. Rule 13.2 defines the method for determining whether the requirement of unity of invention is satisfied in respect of a group of inventions claimed in an international application. Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding "special technical features". The expression "special technical features" is defined in Rule 13.2 as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art. The determination is made on the contents of the claims as interpreted in light of the description and drawings (if any)."
>
> .....
>
> "(f) "Markush Practice." The situation involving the so-called "Markush practice" wherein a single claim defines alternatives (chemical or non-chemical) is also governed by Rule 13.2. In this special situation, the of a technical interrelationship and the same or corresponding special technical features as defined in Rule 13.2, shall be considered to be met when the alternatives are of a similar nature."
>
> "(i) When the Markush grouping is for alternatives of chemical compounds, they shall be regarded as being of a similar nature where the following criteria are fulfilled:
>
> (A) all alternatives have a common property or activity, and
> (B)(1) **a common structure is present, i.e., a significant structural element is shared by all of the alternatives**, or
>
> (B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains."
>
> "(ii) In paragraph (f)(i)(B)(1), above, the words "significant structural element is shared by all of the alternatives" refer to cases where **the compounds share a common chemical structure which occupies a large portion of their structures**, or in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of existing prior art, and the common structure is essential to the common property or activity. The structural element may be a single component or a combination of individual components linked together."
>
> (iii) In paragraph (f)(i)(B)(2), above, the words "recognized class of chemical compounds" mean that there is an expectation from the knowledge in the art that members of the class will behave in the same way in the context of the claimed invention. In other words, each member could be substituted one for the other, with the

expectation that the same intended result would be achieved.

(iv) The fact that the alternatives of a Markush grouping can be differently classified shall not, taken alone, be considered to be justification for a finding of a lack of unity of invention.

(v) When dealing with alternatives, if it can be shown that at least one Markush alternative is not novel over the prior art, the question of unity of invention shall be reconsidered by the examiner. Reconsideration does not necessarily imply that an objection of lack of unity shall be raised.

(Applicants' emphases)

37 CFR § 1.499 ("Unity of invention during the national stage") states:

"If the examiner finds that a national stage application lacks unity of invention under § 1.475, the examiner may in an Office action require the applicant in the response to that action to elect the invention to which the claims shall be restricted. Such requirement may be made before any action on the merits but may be made at any time before the final action at the discretion of the examiner. Review of any such requirement is provided under §§ 1.143 and 1.144."

37 CFR § 1.475 ("Unity of invention before the International Searching Authority, the International Preliminary Examining Authority and during the national stage") states:

"(a) An international and a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art."

MPEP 803.04 ("Nucleotide Sequences") states:

"Nevertheless, to further aid the biotechnology industry in protecting its intellectual property without creating an undue burden on the Office, the *>Director< has decided *sua sponte* to partially waive the requirements of 37 CFR 1.141 et seq. and permit a reasonable number of such nucleotide sequences to be claimed in a single application. See Examination of Patent Applications Containing Nucleotide Sequences, 1192 O.G. 68 (November 19, 1996).'

'It has been determined that normally ten sequences constitute a reasonable number for examination purposes. Accordingly, in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction.'

MPEP 1850 ("Unity of Invention Before the International Searching Authority") states:

> "¶ 18.07.03 Heading - Chemical Compound Alternatives of Markush Group Are Not of a Similar Nature"
>
> "Where a single claim defines alternatives of a Markush group, the requirement of a technical interrelationship and the same or corresponding special technical features as defined in Rule 13.2, is considered met when the alternatives are of a similar nature. When the Markush grouping is for alternatives of chemical compounds, the alternatives are regarded as being of a similar nature where the following criteria are fulfilled:
>
> (A) all alternatives have a common property or activity; AND
>
> (B)(1) a common structure is present, that is, a significant structural element is shared by all of the alternatives; OR
>
> (B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains."
>
> "The phrase "significant structural element is shared by all of the alternatives" refers to cases where the compounds share a common chemical structure which occupies a large portion of their structures, or in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of existing prior art, and the common structure is essential to the common property or activity."
>
> "The phrase "recognized class of chemical compounds" means that there is an expectation from the knowledge in the art that members of the class will behave in the same way in the context of the claimed invention, i.e. each member could be substituted one for the other, with the expectation that the same intended result would be achieved."

Applicants respectfully submit that the Examiner has not shown that the instant claims must be subjected to restriction and election of species under 37 CFR § 1.475(d) since both the ISR and the IB did not indicate that the application from which the instant US application filed under 35 USC § 371 claims benefit lacked unity of invention.

Applicants have enclosed copies of the International Search Report of the ISA/US (mailed 18 November 2005), the Written Opinion of the ISA/US (mailed 18 November 2005), and the International Preliminary Report on Patentability of the IB (mailed 15 June 2006) showing that the both the ISA and the IB indicated that the International Application designating the United States did not "Lack Unity of Invention" (see ISR page 1, section 3, box unchecked; Written Opinion of the ISA page 3, section 1, Box No. IV unchecked; and IPRP page 2, section 3, Box No. IV unchecked).

Applicants respectfully submit that the ISA/US found that the application complied with the "Unity of Invention" requirements so linked as to form a single general inventive concept under PCT Rule 13.1. Applicants further respectfully submit that since the requirements of PCT Rule 13.1 were met, the claims at issue complied with 37 CFR §§ 1.475 and 1.499.

As such, in response to the Restriction Requirement Applicants provisionally elect Group II (claims 5-10, 15-16, 22-23, 25-26, and 28-29).

Species Election

The Examiner stated that Applicant is further required under 35 UCS § 121, (1) to elect a single disclosed species to which claims would be restricted if no generic claim is finally held to be allowable and (2) to list all claims readable thereon including those subsequently added.

The Examiner stated that a specific antibody comprising an amino acid residue sequence such as SEQ ID NO: 8, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, or SEQ ID NO: 31, are distinct species because their structures and modes of action are different which, in turn, address different therapeutic endpoints.

In response to the Examiner's request, Applicants hereby provisionally elect the species of: (B) an antibody comprising a complementarity determining region comprising SEQ ID NO: 26, claims 5-10, 15-16, 22-23, 25-26, and 28-29, with traverse.

Applicants respectfully submit that all alternatives have a common property or activity and a common structure is present, that is, a significant structural element is shared by all of the alternatives as discussed below. (See MPEP 1850; PCT Rule 13.2, Annex B, (f)(i)(B)(1) and (f)(ii); 37 CFR § 1.475; 37 CFR § 1.499.)

Applicants herewith list the amino acid residue sequence of SEQ ID NO: 8, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, and SEQ ID NO: 31.

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SEQ ID NO: 8  Val Arg Val Val Cys Arg Ala Asp Arg Arg Cys Tyr Ala Met Asp Val
SEQ ID NO: 25 Val Arg Val Val Cys Arg Ala Asp Lys Arg Cys Tyr Ala Met Asp Val
SEQ ID NO: 26 Val Arg Val Trp Cys Arg Ala Asp Arg Arg Cys Tyr Ala Met Asp Val
SEQ ID NO: 27 Val Arg Val Trp Cys Arg Ala Asp Lys Arg Cys Tyr Ala Met Asp Val
SEQ ID NO: 28 Val Gly Val Val Cys Arg Ala Asp Arg Arg Cys Tyr Ala Met Asp Val
SEQ ID NO: 29 Val Gly Val Val Cys Arg Ala Asp Lys Arg Cys Tyr Ala Met Asp Val
SEQ ID NO: 30 Val Gly Val Trp Cys Arg Ala Asp Arg Arg Cys Tyr Ala Met Asp Val
SEQ ID NO: 31 Val Gly Val Trp Cys Arg Ala Asp Lys Arg Cys Tyr Ala Met Asp Val
                1               5                  10                  15
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Applicants respectfully submit that careful inspection of each peptide sequence shows that the peptides only differ at positions 4 and 9 where the residue is alternately Val/Trp and Arg/Lys and that were determined as a consensus sequence by careful experimentation (see specification at page 8, lines 27-32 and at page 33, Table 2). Applicants submit that Table 2 at page 12 of the specification as filed shows that arginine and lysine may be substituted for one another as a conservative substitution. Applicants also disclosed that substitutions may be made that are less conservative at page 13, lines 1-5, e.g. valine and tryptophan.

Applicants draw the Examiner's attention to the Application at Figure 5A where the effects of a synthetic peptide comprising SEQ ID NO: 26 or SEQ ID NO: 30 inhibits platelet aggregation at between 9 μm and 90 μM compared with control sample (no addition). Applicants submit that SEQ ID NO: 26 and SEQ ID NO: 30 both comprise the peptide sequence VWCRADRRC. In addition, Figures 5B and 5C show that synthetic peptides comprising SEQ ID NOs: 8 or 28 and 27 or 31, respectively, also inhibit platelet aggregation at between 9 μm and 90 μM compared with control sample. Applicants submit that SEQ ID NO: 8 and SEQ ID NO: 28 both comprise the peptide sequence VVCRADRRC and that SEQ ID NO: 27 and SEQ ID NO: 31 both comprise the peptide sequence VWCRADKRC.

Applicants submit that although the structures are different, in view of the similar effects that the different peptides have upon inhibition of platelet aggregation as disclosed in Figure 5, the differences in structures do not result in a different mode of action, contrary to the Examiner's assertions.

Applicants respectfully note that MPEP 803.04 permits up to ten nucleotide sequences constitute a reasonable number for examination purposes. Applicants submit that the eight peptide sequences recited in claims 5 and 16, also constitute a reasonable number for examination purposes.

In addition, Applicants respectfully submit that the species recited in claims 5-10, 15-16, 22-23, 25-26, and 28-29 are each members of a single Markush group. Applicants respectfully draw the Examiner's attention to MPEP 2173.05(h) that states:

> Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. The materials set forth in the Markush group ordinarily must belong to a recognized physical or chemical class or to **an art-recognized class**; when the Markush group occurs in a claim reciting a process or a

> combination (not a single compound), it is sufficient if the members of the group are disclosed in the specification to possess at least one property in common which is mainly responsible for their function in the claimed relationship, and it is clear from their very nature or from the prior art that all of them possess this property.
> (Applicants' emphasis)

Applicants submit the claimed antibodies belong to an art-recognized class of antibodies that specifically immunoreact with integrin $\alpha_{IIB}\beta_3$ and comprise an amino acid residue sequence selected from the group consisting of SEQ ID Nos: 8, 25, 26, 27, 28, 29, 30, and 31, wherein the amino acid residue sequence is within a complementarity determining region (CDR) of the antibody (see specification at page 3, lines 18-25). Furthermore, they posses at least one property in common, that property being "specifically immunoreacts with integrin $\alpha_{IIB}\beta_3$" (see, for example, specification at page 27, lines 1-3 and 9-10 and Figure 3B).

MPEP 803 states:

> If the search and examination of all the claims in an application can be made without serious burden, the examiner must examine them on the merits, even though they include claims to independent or distinct inventions.

MPEP 803.02 states:

> If the members of the Markush group are **sufficiently few in number or so closely related** that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they may be directed to independent and distinct inventions. In such a case, the examiner will not follow the procedure described below and will not require provisional election of a single species. (Applicants' emphasis)

Applicant submits that the members of the genus are sufficiently few in number and are so closely related that a search and examination of the claims can be made without a serious burden and that the claims must be examined on the merits.

Applicant respectfully affirms that proper Markush language is recited in claims 5-10, 15-16, 22-23, 25-26, and 28-29 and that claims 5-10, 15-16, 22-23, 25-26, and 28-29 conform to MPEP 803.02. Applicants request the Examiner reconsider the requirement for an election of a species.

The Examiner is respectfully reminded that, upon allowance of the claims to the above antibody, a second process using the antibody, i.e., the claims of Group V (claims 12, 14, and 31-32) must be rejoined. See the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products.

Applicants have included a petition for an extension of time of one month to respond to the Examiner's Restriction Requirement with this response. However, if the USPTO determines that an additional fee is due, the Commissioner is hereby authorized to charge Bell & Associates' Deposit Account No. **50-3194.**

Respectfully submitted,

Date: 18th December 2010

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